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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/091,061
Filing Date: March 05, 2002
Appellant(s): LEE, FRANCIS Y.F.

Anastasia Winslow
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 5/30/2006 appealing from the Office action mailed 12/27/2005.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings, which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of the claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

The following is a listing of the evidence (e.g., patents, publications, Official Notice, and admitted prior art) relied upon in the rejection of claims under appeal.

Danishefsky (US Patent 6,867,305)

Miwa et al. (European Journal of Cancer, vol. 34, no. 8, pp. 1274-1281, 1998)

Vite (WO 99/02514)

The Merck Index (12th Edition, pp. MISC-10, 1996)

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims 117-130 only:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 102-104, 112, and 117-125 are rejected under 35 U.S.C. 103(a) as being unpatentable over Danishefsky et al. (US 6867305) in view of Miwa et al. European Journal of Cancer (1998), 3448), 1274-1281, of record).

Danishefsky et al. discloses that administering a pharmaceutical composition comprising the instant particular compound (see the structure of the compound at col.108 lines 29-45) also known as C-15-Aza-EpoB (see Figure 33), azaepothilone b or ixabepilone to a mammal, is useful in methods of treating one or more of cancers such as cancerous solid tumors, refractory tumors, metastatic breast cancer, lung cancer, prostate cancer, and pancreatic cancer and methods for the treatment of cancer which has developed a muti-drug resistance (MDR) (see abstract, col. 59 lines 27-44).

In particular, the compounds of Danishefsky et al. such as the instant compound have been found effective not only reversing muti-drug resistance (MDR) in cancer cells both in vitro or in vivo, e.g., resistant to taxane treatment (paclitaxel or Taxol), but also more cytotoxic towards MDR cells than normal cells and as synergistic agents, which are more active in combination with other cytotoxic agents or anticancer agents than the individual drugs alone (see col.30 lines 15-32; col.59 line 45-59). Those other cytotoxic agents or anticancer agents such as 5-fluorouracil (5-FU) are used in combination with the instant compounds (see col.59 line 60 to col.60 line 7).

The combination compositions of the instant compound and the other cancer drug can be administered substantially and simultaneously (concurrently) to humans or animals orally (see col.59 line 45-59., col. 57 lines 8-10) in various dosage forms (col.56-57).

Note that Danishefsky et al. discloses that the effective amount of the instant compound to be administered is in the range of about 0.01 ma to 50 mg/kg/day or 1 mg to 25 mg/kg/day (see col.57 lines 20-24), which are same or overlapping with the effective amounts, indicated in Applicant's specification (see page 39-41 of the specification).

Danishefsky et al. does not expressly disclose the employment of capecitabine in combination with the instant particular compound in a pharmaceutical composition and a method for treating cancer.

Miwa et al. discloses that capecitabine (N4-pentyloxycarbonyl-5'-deoxy-5-fluorocytidine), which is finally converted to 5-fluorouracil (5-FU) by dThdpase in

tumors, should be much safer and more effective than 5-FU, for treating cancers or various types of tumors. See abstract and the entire article.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ capecitabine in combination with the instant particular compound in a pharmaceutical composition and a method for treating cancer.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ capecitabine in combination with the instant particular compound in a pharmaceutical composition and a method for treating cancer, since, first, 5-fluorouracil is known to be useful in combination with the instant particular compound in a pharmaceutical composition for methods for treating cancer effectively and synergistically, according to Danishefsky et al.

Second, capecitabine (N4-pentyloxycarbonyl-5'-deoxy-5-fluorocytidine), is known to be much safer and more effective than 5-FU and finally converted to 5-fluorouracil (5-FU) by dThdPase in tumors.

Therefore, one of ordinary skill in the ad would have reasonably expected that combining capecitabine in combination with the instant particular compound in a pharmaceutical composition for methods for treating cancer, would have been much safer and even more effective than the combination of 5-FU and the instant compound in treating the same.

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Claims 101-130 are rejected under 35 U.S.C. 103(a) as being unpatentable over

Vite et al. WO 99/02514, of record) in view of The Merck Index, (12th ED), 1996, and Miwa et al. European Journal of Cancer (1998), 3448), 1274-1281 essentially for same reasons of record stated in the Office Action dated November 17, 2004.

Vite et al. discloses that the instant particular compound (see Example 3 at page 48) is useful in treating various types of cancers or tumors including the cancers recited in the instant claims 105-110 (see page 8-10). More important, Vite et al. discloses that the instant compound is useful in combination with known anti-cancer and cytotoxic agents for cancer treatment. See page 10.

The prior art does not expressly disclose the employment of the instant particular compound in combination with the specific anti-cancer agents such as fluorouracil (5-FU) and/or capecitabine in a pharmaceutical composition and a method for treating cancer.

The Merck Index teaches that fluorouracil (5-FU) is well-known to be used in combination cancer chemotherapy, i.e., combing with other anti-cancer agents as cancer chemotherapy drug regimens (see MISC-10).

Miwa et al. discloses that capecitabine (N4-pentyloxycarbonyl-5'-deoxy-5-fluorocytidine), which is finally converted to 5-fluorouracil (5-FU) by dThdPase in tumors, should be much safer and more effective than 5-FU, for treating cancers or various types of tumors. See abstract and the entire article.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ the instant particular compound in combination with the specific anti-cancer agents such as fluorouracil (5-FU) and/or capecitabine in a

pharmaceutical composition and a method for treating cancer.

One having ordinary skill in the ad at the time the invention was made would have been motivated to employ the instant particular compound in combination with the specific anti-cancer agents such as fluorouracil (5-FU) and/or capecitabine in a pharmaceutical composition and a method for treating cancer, since the instant adicular compound is known to be useful in treating various types of cancers or tumors including the cancers herein and also useful in combination with known anti-cancer and cytotoxic agents for cancer treatment according to Vite et al.

Moreover, fluorouracil (5-FU) is well-known to be used in combination cancer chemotherapy according to The Merck Index. Capecitabine (N4-pentyloxycarbonyl-5'-deoxy-5-fluorocytidine), is known to be finally conrteded to 5-fluorouracil (5-FU) by dThdPase in tumors, and should be much safer and more effective than 5-FU, for treating cancers or various types of tumors according to Miwa et al.

Therefore, one of ordinary skill in the art would have reasonably expected that combining the specific anti-cancer agents such as fluorouracil (5-FU) and/or capecitabine and the instant compound, both known useful for the same purpose, i.e., treating cancers, would improve the therapeutic effects for treating the same, and/or would introduce additive therapeutic effects in treating the same.

It has been held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose, idea of combining them flows logically from their having been individually taught in prior art. See In re Kerkhoven, 205

USPQ 1069, CCPA 1980.

Further, the teachings of Vite et al. that the instant compound is useful in combination with known anti-cancer and cytotoxic agents for cancer treatment, and the combination cancer chemotherapy drug regimens in Merck Index, have clearly provided the motivation for the combination claimed herein.

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

(10) Response to Argument

Appellant argues that there is no motivation or reasonable expectation of success to combine the prior art references because Danishefsky discloses, but teaches against, the use of epothilone B (1b, aza-EpoB) or compound (1) of the present invention. Specifically, excerpts regarding aza-EpoB as having a less therapeutic profile and reduced activity than other epothilone analogs disclosed by Danishefsky are used as support.

This argument is not persuasive because the standard for a case of obviousness is not absolute success but a reasonable expectation of success. Although Danishefsky discloses a better epothilone analog, there is no question that aza-EpoB possesses therapeutic activity and thus is useful for treating cancer. This is supported by Danishefsky where aza-EpoB inhibited tumor growth but did not lead to a reduction in the size of the tumor is disclosed (col. 99, lines 54-59).

Appellant also argue that Danishefsky teaches whereas aza-EpoB was more active than dEpoB in nonresistant cell lines, it proved ineffective when extended to in

vivo models. This argument is not persuasive because Appellant cannot attack prior art references individually. Nonetheless, Danishefsky clearly teaches that aza-EpoB can inhibit tumor growth as discussed above.

In response to applicant's arguments against the references, one cannot show nonobviousness by attacking references individually where the rejections are based on the combination of references. See *In re Keller*, 642 F. 2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F. 2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Appellants argue hindsight reconstruction by picking and choosing both compound (1) and specific anticancer agent (5-FU) from a multitude of compounds as disclosed in the Danishefsky and Vite prior art references.

Examiner argues that Danishefsky clearly discloses aza-EpoB as more active in combination with other cytotoxic agents or anticancer agents than the individual drugs alone (see col.30 lines 15-32; col.59 line 45-59). Those other cytotoxic agents or anticancer agents such as 5-fluorouracil (5-FU) are used in combination with the instant compounds (see col.59 line 60 to col.60 line 7). Vite also discloses that the compound (1) is useful in combination with known anti-cancer and cytotoxic agents for cancer treatment (pg 10). Therefore, a reasonable expectation of success has been established for the choosing this particular combination.

Appellant argues that there is no motivation by Miwa to interchange capecitabine with 5-FU. Appellant has also provided various publications counseling against combinations of 5-FU and other microtubule-stabilizing agents, such as paclitaxel.

Examiner respectfully remind Appellant that Miwa discloses capecitabine to be converted to 5-fluorouracil (5-FU) by dThdpase in tumors, should be much safer and more effective than 5-FU, for treating cancers or various types of tumors (abstract). Moreover, the other articles are not relevant because it is specifically referring to the combination of 5-FU and other microtubule-stabilizing agents, such as paclitaxel, which is not claimed in the instant invention or the prior art references.

Finally, Appellant argues for the surprisingly synergistic effect for the combination of compound (1) and capecitabine as evidenced in the Declaration.

Examiner respectfully argues that the Declaration is not relevant because it is not commensurate with the scope of the claims on several key points. Firstly, the claims are drawn various cancers, of which the Declaration has support for only colon cancer. Secondly, there is only one data point in the Declaration drawn to 10 mg/kg of compound (1) and 250 mg/kg/adm of capecitabine, whereas the claims are drawn to all dosage ranges of both compound (1) and capecitabine. Thirdly, the results of the Declaration clearly provide only a delay in tumor growth, while the claims are drawn to treating cancer, which is construed as both inhibition and regression of cancer.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Yong S. Chong, Ph.D.
Patent Examiner
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ysc
July 12, 2006

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